

# An exploratory Olink proteomic analysis identifies thrombopoietin as the predominant protein altered during selinexor maintenance

THE RESULT

THPO

the sole protein of 1,033 to clear correction ·  $q = 2.33 \times 10^{-4}$

+1.197

$\log_2$  NPX

1 / 1,033

proteins clearing 5% FDR

19 / 19

selinexor-arm patients with increased THPO

## 01 INTRODUCTION

Selinexor is an antineoplastic agent that blocks exportin-1 (XPO1), the karyopherin that exports over two hundred cargoes from the nucleus [1]. Because XPO1 is expressed in malignant and healthy tissue alike, selinexor has a broad adverse-effect profile.

ALLG MM23 (SeaLAND) tested weekly selinexor added to lenalidomide maintenance after autologous stem cell transplantation (ASCT) in multiple myeloma. It stopped early for futility (HR 1.14,  $p = 0.69$ ), with grade  $\geq 3$  thrombocytopenia in 26% of the selinexor arm versus 2% of controls [2].

THE GAP LEFT BEHIND BY THE ALLG MM23 TRIAL

ALLG MM23 tested whether selinexor improved outcomes, not its systemic proteomic effects, which this study set out to characterise.

## 02 OBJECTIVES

- 1 Measure the systemic effect of six months of selinexor on the plasma proteome, with no protein nominated a priori.
- 2 Test whether any protein changes differently between arms after correction for multiple testing.
- 3 Interpret any significant finding in the context of known physiology.

## 03 METHODS

### Samples

38 patients (19 per arm), with paired plasma after ASCT and at six months.

### Measurement

One Olink Reveal plate: 1,034 assays, 1,033 passing quality control. NPX (Normalised Protein eXpression) is a relative  $\log_2$  scale; one unit is a two-fold difference.

### Analysis

Within-patient changes were compared between arms using a difference-of-differences model in limma, with patient blocking.

$$\Delta \text{NPX} = \text{NPX}(\text{6 months}) - \text{NPX}(\text{baseline})$$

### Significance

Benjamini–Hochberg false-discovery rate of 5%, with robustness tested by 20,000 label permutations, 38 leave-one-out refits and six sensitivity re-analyses.

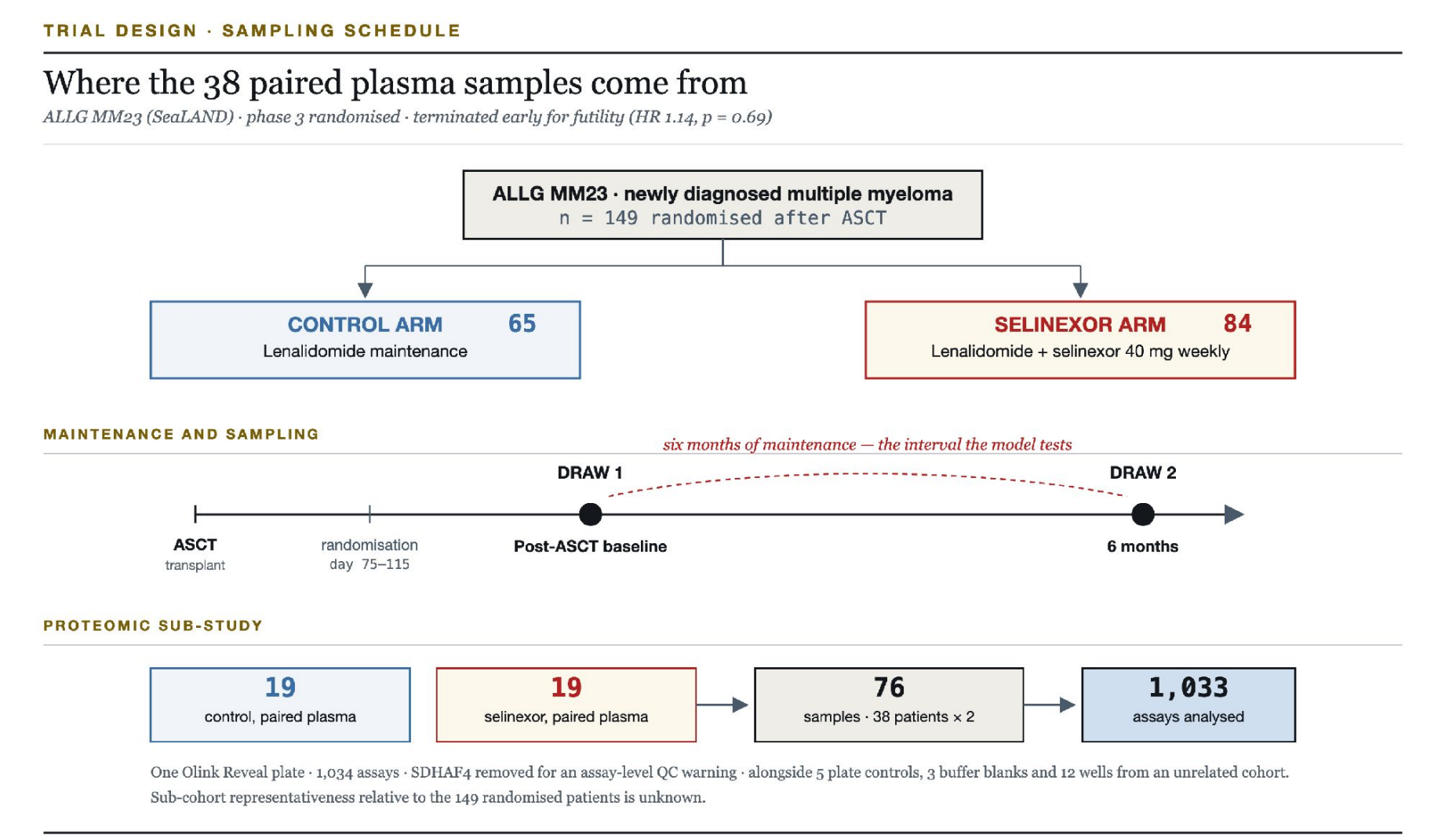


FIG. 1 Trial design and sampling. Both arms received lenalidomide; selinexor was added in one.

## 04 RESULTS

### One of 1,033 proteins remained significant

167 proteins reached  $p < 0.05$ , against 52 expected by chance. After Benjamini–Hochberg correction only thrombopoietin (THPO) remained significant ( $+1.197 \log_2$ ,  $q = 2.33 \times 10^{-4}$ ).

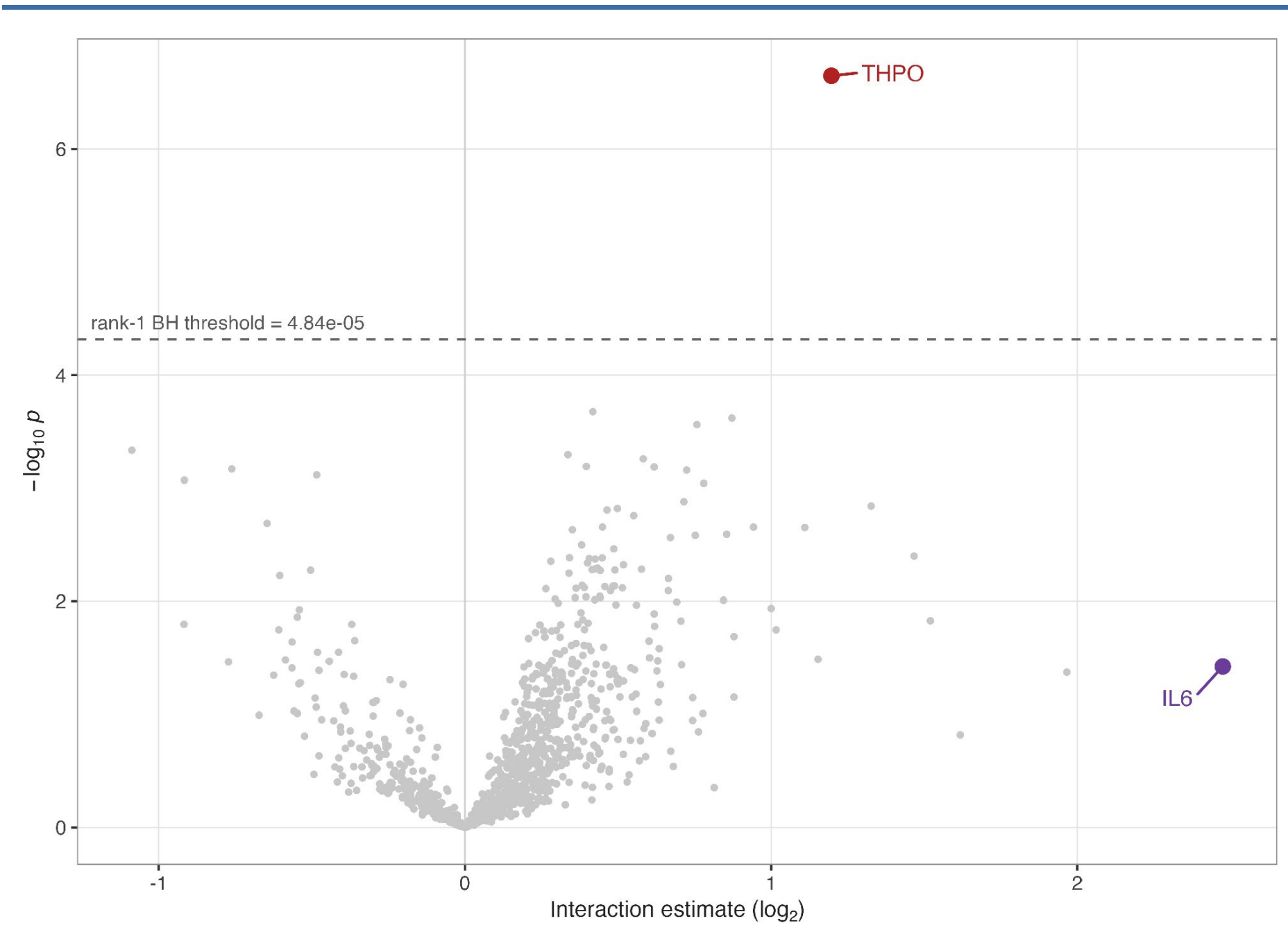


FIG. 2 Effect against  $p$  for all 1,033 proteins. Only THPO clears correction; IL-6 has the largest effect and uncertainty.

### THPO increased in every selinexor-arm patient

All 19 selinexor-arm patients showed an increase in THPO (median  $+1.013 \log_2$ , about two-fold). In controls, 9 of 19 increased and 10 decreased, so their mean of  $-0.023 \log_2$  reflects offsetting changes, not an absence of change.

THPO change separated the arms with an AUC of 0.945, the highest of all 1,033 proteins: a randomly chosen selinexor-arm patient had a larger increase than a randomly chosen control 94.5% of the time.

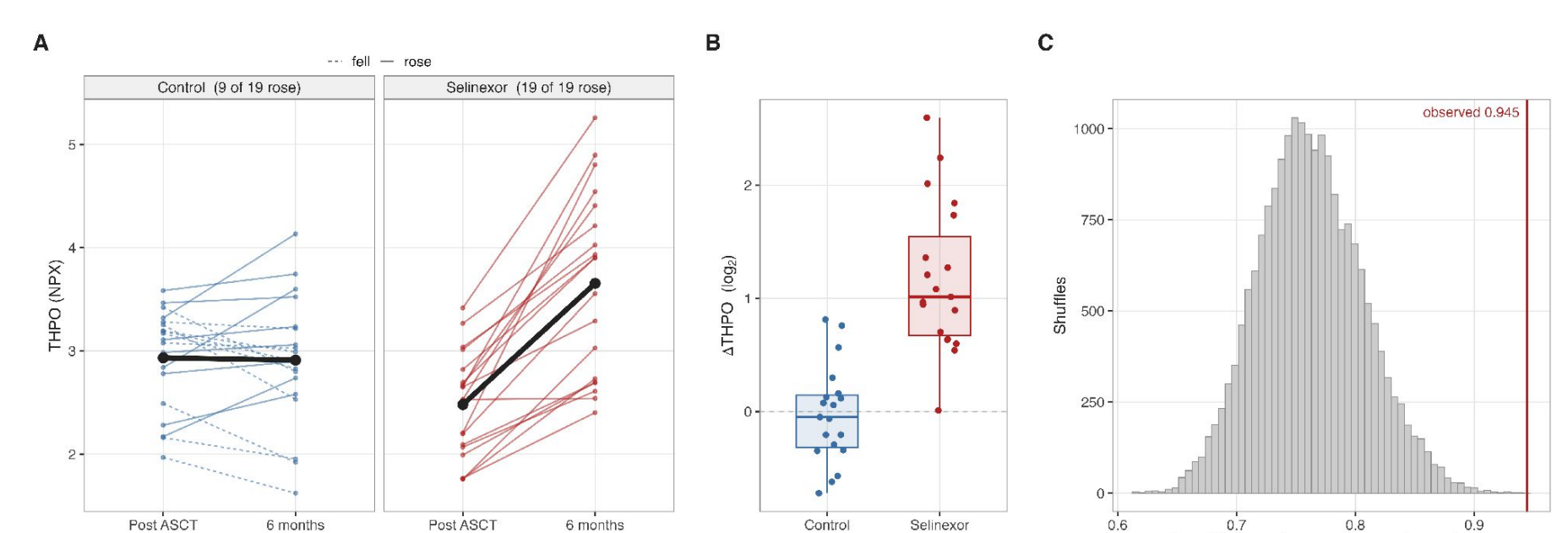


FIG. 3 (A) THPO per patient by timepoint. (B) Change by arm. (C) Null distribution from 20,000 label permutations.

SENSITIVITY

Six sensitivity re-analyses of the same 38 patients gave  $+1.037$  to  $+1.332 \log_2$ .

### The single grade $\geq 3$ thrombocytopenia event

One selinexor-arm patient had a recorded grade  $\geq 3$  thrombocytopenia event. Their THPO increase ( $+0.895 \log_2$ ) was below the arm median; 12 patients without an event increased more.

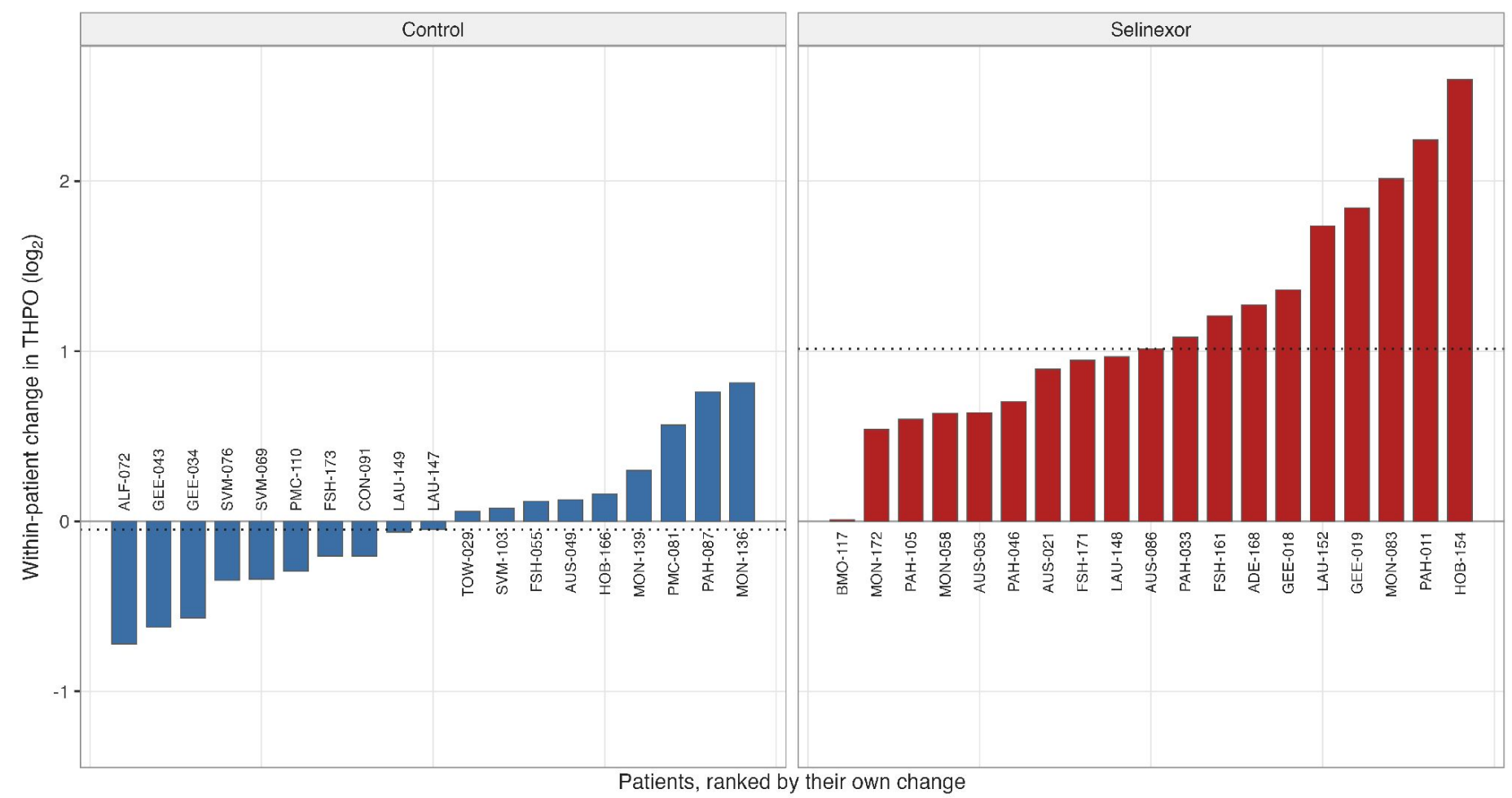


FIG. 4 THPO change per patient, ranked within arm. The patient with the recorded event did not have the largest increase.

## 05 DISCUSSION

### A tap and a drain

Plasma THPO reflects a balance between hepatic production (the tap) and c-Mpl-mediated clearance by platelets, megakaryocytes and progenitors (the drain) [3–6]. A rise may reflect either.

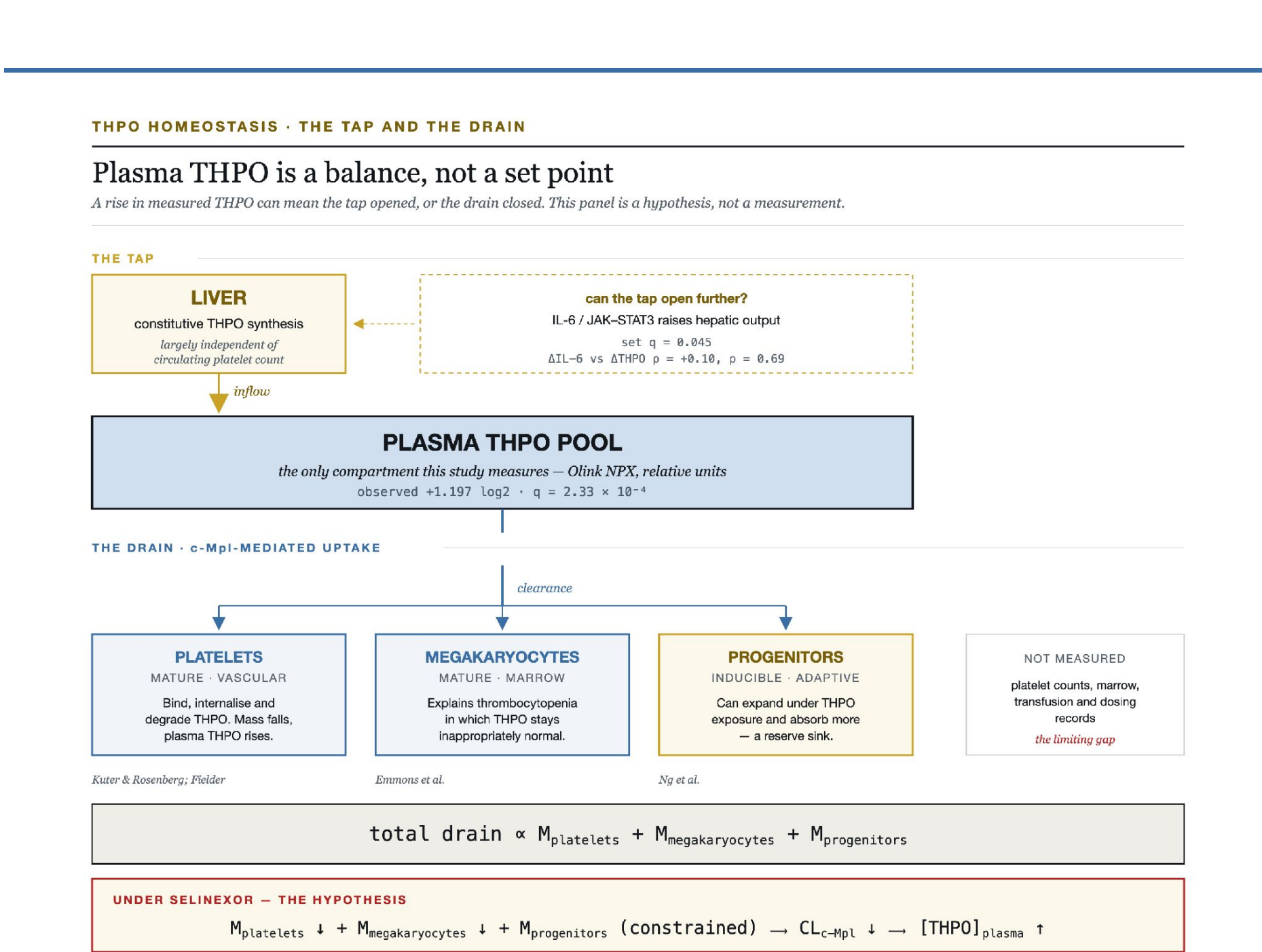


FIG. 5 The tap-and-drain model of plasma THPO and the proposed site of selinexor action.

In mice, selinexor inhibits thrombopoietin signalling in early megakaryopoiesis [7]. Fewer megakaryocytes and platelets would reduce clearance and could raise plasma THPO.

### Could inflammation explain it?

Inflammatory and IL-6/JAK–STAT3 gene sets were enriched, and IL-6 stimulates hepatic THPO production [8], but  $\Delta$ IL-6 and  $\Delta$ THPO did not correlate in either arm.

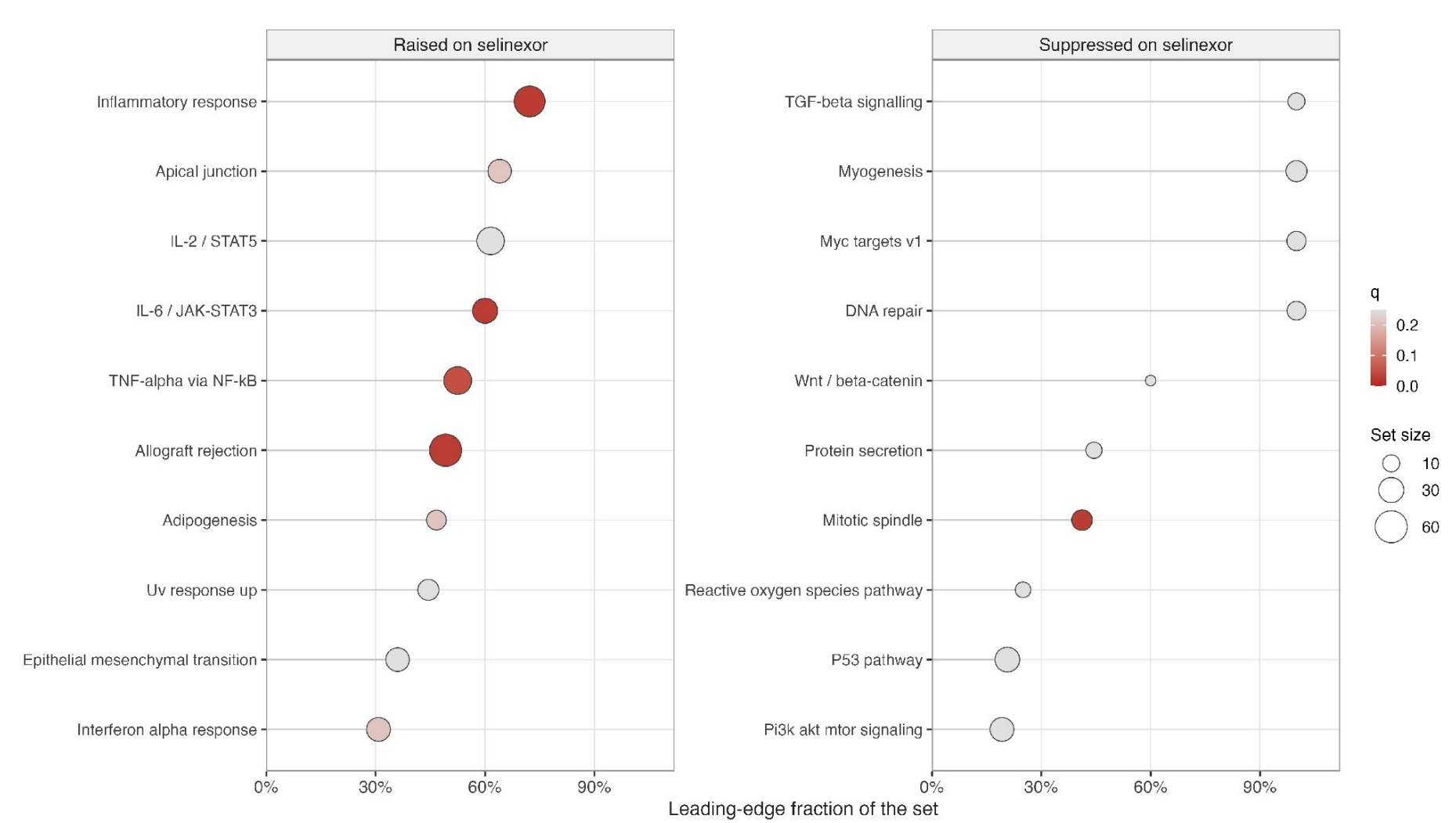


FIG. 6 Hallmark gene sets by leading-edge fraction; exploratory and not corrected for the panel's bias toward secreted proteins.

## 06 CONCLUSIONS

- Of 1,033 proteins, only THPO changed significantly differently between arms, and it increased in all 19 selinexor-arm patients.
- The result held across all sensitivity analyses and permutation tests.
- These data cannot distinguish reduced clearance from increased production.
- All mechanistic interpretation is hypothesis-generating.

## 07 LIMITATIONS

Small post hoc sub-cohort ( $n = 38$ ) with two timepoints. No serial platelet counts, event timing or concomitant medication records. NPX is relative, so production and clearance cannot be separated. Selinexor exposure varied (mean relative dose intensity 55%).

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